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Original research

Imaging of adrenal incidentaloma: Our experience

Alfonso Reginelli [a, *], Graziella Di Grezia [a], Andrea Izzo [a], Alfredo D'andrea [a], Gianluca Gatta [a], Salvatore Cappabianca [a], Ettore Squillaci [b], Roberto Grassi [a]

[a] Department of Internal and Experimental Medicine, Magrassi-Lanzara, Institute of Radiology, Second University of Naples, Piazza Miraglia 2, 80138 Napoli, Naples, Italy

[b] Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome Tor Vergata, Rome, Italy

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ABSTRACT

Purpose: To investigate clinical, biochemical and radiological features in 35 patients with adrenal incidentaloma found on CT and/or MRI and to define the management of patients with adrenal masses.

Matherial and methods: From January 2011 and May 2013, 35 patients (19F, 16M) with an adrenal mass incidentally discovered on CT and/or MRI were enrolled in a retrospective study. Thirthy-two patients underwent MDCT and eight 1.5 MRI.

Results: Patients consisted in 16 males and 19 females, aged between 25 and 89 yo. Adrenal lesions were most commonly found in the sixth decade; in relation to the side of the mass, 20 were found on left side, 15 on the right. Of all the mass analyzed, 3 were <1 cm diameter, 29 between 1 and 4 cm, 3 > 4 cm. The most common finding on CT was adenoma-like appearance (19 cases in relation to size, 14 in relation to attenuation values). Hormonal analysis showed 32 cases of nonfunctional masses and 3 cases of hormone activity. Adrenalectomy was performed in ten patients having adenoma (5 cases), malignant lesions (2 cases), pheocromocitoma, cyst and myelolipoma (1 case).

Conclusion: Diagnostic approach to adrenal incidentaloma is focused on the definition of malignancy and hormonal activity; the characterization is needs hormonal and radiological (CT and/or MRI) evaluation, even if a fine needle aspiration is needed in selected cases.

Benign and/or non-hypersecreting hormone lesion with <4 cm diameter could be sent to follow-up; active adrenal tumors or >4 cm diameter lesions with malignancy suspicious or growth during follow-up could be treated with surgical adrenalectomy.

1. Introduction

Adrenal lesions greater than 1 cm detected during non-invasive abdominal imaging techniques performed for unrelated reasons are called "adrenal incidentaloma" or "diseases of modern technology".

The frequency of adrenal incidentaloma has grown with the advancements in imaging technology (US, CT, MRI and scintigraphy); the prevalence increases with age [1], although the higher incidence is reported between 50 and 70 years mainly in patients with diabetes mellitus, hypertension and obesity; there is no difference in prevalence based on race and sex.

The incidence of adrenal nodules at autopsy is between 8.7% [1] and 32% of patients without suspicion of adrenal disease [2–4].

The differential diagnosis includes non-hypersecreting adrenal adenoma, hypersecreting adrenal adenoma (Subclinical Cushing's syndrome, pheocromocitoma, primary aldosteronism), primary adrenal carcinoma, metastases and other adrenal masses (myelolipoma, cyst or ganglioneuroma).

Diagnostical approach includes the differentiation between benign/malignant lesions and functional/nonfunctional lesions; it requires a clinical and biochemical work-up. 80% of adrenal lesions is non-hypersecreting adenoma, with size less than 2 cm [1].

It is necessary to know if the patient has a present or past cancer diagnosis, because in these patients the incidence of malignancy is between 30 and 50% [5]; in patients without history of cancer, malignancy is very rare. There is a correlation also between malignancy and size of the lesion: malignancy suspection increases with the mass diameter [6–8].

Surgery is indicated only in a small fraction of cases, because small and hormonally inactive lesions predominates among suspected masses.

* Corresponding author.
E-mail address: alfonso.reginelli@unina2.it (A. Reginelli).

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Objective of the study is to investigate clinical, biochemical and radiological features in 35 patients with adrenal incidentaloma found on CT and/or MRI and to define the management of patients with adrenal masses.

2. Matherial and methods

2.1. Study population

From January 2011 and May 2013, 35 patients (19F, 16M) with an adrenal mass incidentally discovered on CT and/or MRI were enrolled in a retrospective study.

No subjects who had adrenal mass discovered on these exams presented adrenal symptoms; they had underwent diagnostic exams for other causes, such as abdominal hernias, cholecystitis, other urinary or abdominal symptoms.

Demographic characteristics collected for patients were: sex, age, medical history, diameter and side of the lesion, endocrine function, follow-up and/or histological findings of surgical adrenalectomy.

We also evaluated Hounsfield Units (HU), before and after contrast media administration in benign and malignant lesions at CT exams and Absolute Chemical Shift on MRI.

In relation to endocrine functionality, all patients underwent to hormone tests relating to pheocromocytoma, subclinical Cushing's syndrome, aldosterone primary adenoma.

2.2. Imaging

Thirthy-two patients underwent MDCT (Toshiba, Aquilion 4, Tokyo, Japan) and 8 1.5 MRI (Siemens Symphony 1.5 Erlangen, Germany).

2.2.1. MDCT

The patient was moved to the CT room where scout-view and volumetric scan were carried out. A layer no wider than 3 mm and a reconstructing interval no larger than 5 mm were chosen (kVp: 120, mA: 250; pitch 1).

Iodinated contrast agent was injected intravenously, 1.5 ml iodine/kg body weight (BW) through a mechanic injector at a concentration of 400 mg iodine/mL (contrast agents "Iomeprol" and "Iomeron 400" developed by the Italian pharmaceutical company Bracco) and a flow speed of 2.5 ml/s. The dedicated examination protocol comprise a precontrast CT and two post-contrast scanning (at 35 s and a delayed scanning at 10 min after contrast media injection started).

2.2.2. MRI

All MRI imaging studies were performed on 1.5-T closed magnet (Magnetom Symphony, Siemens, Germany). All patients were supine imaged with a body-phased-array receiver coil.

After an initial localizer in three different planes, the study protocol included:

- T2-W Haste Multiple Breath Hold (MBH), T1-W fl2d in-out of phase, T1-W fl2D Fat suppressed on axial plase; T2-W Haste MBH, T2-W Trufi BH on coronal plane;
- T1-W FLASH 3D Fat suppressed in axial plane, before contrast media administration;
- 4 sequential scans with 20 s interval and tardive acquisition 10 min after (T1-W FLASH 3D Fat Suppressed in axial plane after Gd-DTPA (0.1 mmol/kg).

During post-processing examination, Region of Interest (ROI) were used for densitometric evaluation on CT exam and signal intensity in in-out of phase MRI; ROI were realized in relation to lesion diameter excluding calcifications and or fluid areas on CT and/or MRI.

ROI value of intensity signal on T1-W fl2d in-out phase to calculate Absolute Chemical Shift (ACS) were included in the form:

$$[(\mathrm{SIIP}-\mathrm{SIOP})/\mathrm{SIIP}]\times 100$$

[SIIP: signal intensity in phase; SIOP: signal intensity out of phase]

3. Results

Of 35 patients, three were <40 yo, seven between 40 and 50 yo, twelve between 50 and 60 yo, ten between 60 and 70 yo, 3 over >70 yo. Adrenal lesions are more frequent in the age between 50 and 70 yo.

There were 19 females, 16 males; 27 patients underwent MDCT, 3 MRI, 5 underwent MDCT and MRI and one patient underwent also scintigraphy.

Of the 35 lesions detected, 20 were on left side, 15 on the right side; no bilateral lesions were detected; 3 were functional, 32 were nonfunctional masses (Table 1).

In relation to lesion diameter, 3 were <1 cm, 29 with a size between 1 and 4 cm, 3 presented a diameter >4 cm.

The location, size and shape of lesions were determined with CT and MRI and it was found that 19 subjects had features of adenoma; 18 of these 19 patients were less than 4 cm in size.

Cushing syndrome was detected in 4 patients, pheocromocitoma in 5, malign lesion and myelolipoma in one case (Table 2).

Measurement of HU by nonenhanced CT yielded 7 subjects and 3 subjects out of 14 patients with adenoma-like appearance with less than 10 HU and over 20 HU, respectively.

Conversely, measurement less than 10 HU and between 10 and 20 HU were observed in the two patients with pheocromocitoma-like appearance lesions (Table 3).

Semiquantitative study of Pre and Postcontrast media injection on MDCT at 35 s (wash in) and 10 min (wash-out) and absolute Chemical Shift in MRI with a cut-off of 16.5%, demonstrated substantial differences, as shown in Table 4.

Patients with <4 cm diameter adrenal lesions, with endocrine negative tests, were sent to follow-up with CT after 3–6 months and then every year for three years with endocrine reevaluation every year.

Table 1
Characteristics of 35 adrenal incidentaloma.

Characteristics	No
Age (yo)	
<40	3
40–50	7
50–60	12
60–70	10
>70	3
Sex	
Male	16
Female	19
Site	
Right	15
Left	20
Bilateral	0
Functionality	
Yes	3
No	32
Exams	
CT	27
MRI	3
CT and MRI	5
Scintigraphy	1

Table 2
Distribution of clinical diagnosis by mass size.

Diagnosis	TOT	<1 cm	≥1 cm	>4 cm
Adenoma	19	2	16	1
Subclinical cushing's syndrome	4		4	
Primary aldosteronism	3		3	
Pheocromocitoma	5	1	3	1
Malignant lesion	2		1	1
Myelolipoma	1		1	
Cyst	1		1	
Other	0			
Total	35	3	29	3

Patients with >4 cm diameter adrenal mass or irregular margin and density or intensity regular shape and patients with >4 cm lesion with positive endocrine tests or increase in tumor size during follow-up were sent to surgical adrenalectomy.

Of ten patients underwent surgical adrenalectomy, adenoma was the most frequent case, with 5 lesions, followed by 2 cases with malignant lesion, 1 case of pheocromocitoma, 1 of cyst and 1 of myelolipoma.

A total of two patients underwent surgery as treatment for functional masses, three for suspected malignancy, one for lesion size (>4 cm), and four underwent adrenalectomy concurrent with nonadrenal surgery (Table 5).

4. Discussion

The diagnostic approach of adrenal incidentaloma aims to determine the type of mass and focuses of hormonal activity and malignancy suspicious.

4.1. Clinical manifestation

First, a meticulous history is necessary to define hyper, non-hypersecreting lesions, primary adrenal carcinoma, other adrenal masses (myelolipoma, cysts, ganglioneuroma) and metastases.

80% of adrenal incidentaloma are asymptomatic with a size less than 2 cm; in symptomatic lesions, clinical manifestations depends on the type of hormone being secreted by the tumor.

Beacuse 20% of adrenal incidentaloma was asymptomatic hormone hypersecreting tumor, the National Institute of Health suggests to consider all adrenal incidentaloma as hypersecreting tumor, even without clinical manifestation until otherwise proven by hormonal tests [3,9–14]. In addition, the probability of hypersecreting hormone tumor increases with the mass diameter. With a 40% of hypersecreting lesions with >6 cm diameter.

4.2. Laboratory tests

24-h urinary cathecolamines and 1 mg dexamethasone suppression test are performed in patients with imaging diagnosis of adrenal incidentaloma; in patient with hypertension, aldosterone/plasma renin activity ratio is also recommended [2,12–15].

Due to the small number of prevalence of sex-hormone hypersecreting tumor, routine test for sex hormone is not indicated [16–21].

Table 3
Distribution of clinical diagnosis by UH.

Diagnosis	TOT	<10 UH	10–20 UH	>20 UH
Adenoma	14	7	4	3
Subclinical cushing's syndrome	4	2	1	1
Primary aldosteronism	6	3	2	1
Pheocromocitoma	2	1	1	–
Malignant lesion	5	3	–	2
Myelolipoma	2	1	1	–
Cyst	1	–	–	1
Other	1	–	–	1
Total	35	16	9	10

Table 4
HU on pre and post contrast media injection on MDCT. (WI: wash in at 35sec and WO: wash out at 10 min); Absolute Chemical Shift (ACS) and ACS cut-off on CSI –MRI.

	MDCT			CSI MRI	
	Precontrast HU	WI (35 s)	WO (10 min)	ACS (%)	ACS cut-off (%)
Benign lesions	−14 ± 8	70 ± 24	33 ± 21	84 ± 6	≥16.5
Malignant lesions	32.9 ± 7	38.7 ± 15	−10.4 ± 8	−10 ± 19	<16.5

4.3. Imaging techniques

After clinical evaluation and laboratory tests, it is necessary the re-evaluation of imaging features of adrenal masses.

4.3.1. MDCT

Abdomen MDCT is the best choice, especially in relation to cost-effective; the dedicated examination protocol for the characterization of adrenal incidentaloma comprise a pre-contrast CT and two post-contrast scanning (after 35 s and 10 min) [22–25]; in the local practice the post-contrast phases could be performed at different times (90–120 s and 10–15 min) [5].

Homogeneous lesion with smooth margins and size less than 4 cm and density <10 HU without enhancement to contrast media, indicates benign lesions [26–28], with a specificity of 98–99% [29,30]; the presence of macroscopic fat, with a density of −10' HU is characteristic of a myelolipoma; if the attenuation is of 0–15 HU without enhancement after contrast media administration, a simple cyst is suspected [5].

Adrenal lesions with the same attenuation values and an adenoma and/or a cyst appearance with a transverse diameter >4 cm, no further imaging is needed [30]. Tumor size, indeed, is only a supplementary element in CT scan and should not be used as the only element for therapeutic approach [31]; only changes in tumor size during follow-up represent an indication for tumor resection.

On the opposite, precontrast HU value >10 requires information about contrast-enhanced and wash-out. Moderate enhancement followed by a rapid contrast agent washout from the tumors occurs in adenomas [31–33].

Malignant lesions are poor vascularized and have larger interstitial spaces with high pressure; these features prevent the contrast enhancement and delay the contrast medium wash-out [31,34].

On the other side, disomogeneous lesions with irregular shapes, size more than 4 cm, density >10HU and marked enhancement

Table 5
Characteristics of 10 adrenalectomy with a hystopathologic diagnosis proven by surgery.

	>4 cm	Functional mass	Suspected malignancy (>20 UH)	Concomitant surgery	TOT
Adenoma	–	1	–	4	5
Pheocromocitoma	–	1	–	–	1
Malignancy	1	–	1	–	2
Cyst	–	–	1	–	1
Myelolipoma	–	–	1	–	1
Tot	1	2	3	4	10

after contrast administration indicates malignancy [35]. However, myld adenoma or myelolipomas could present inhomogeneity and pheocromocytomas could also contain necrotic areas and calcifications and could present slow wash-out in 10–15 min post-contrast media administration [36].

Usually, a threshold of 10 HU and 24 HU with a 14-min delay on contrast-enhanced CT scan is considered the cut-off to distinguish between adenomas and metastases.

An absolute wash-out in a scanning with a post-contrast delay of 15 min <0.6 indicates a malignant lesion; if the value is >0.6 the lesion may be benign [34,37–39]; in our experience a wash-out HU value of 33 ± 21 is indicative of benign lesions, a value of -10.4 ± 8 is typical of a malignant lesion.

However, in the wash-out calculations, the attenuation measurements may vary depending on technical parameters, such as partial volume effects and how the Region of Interest (ROI) is drawn and positioned.

4.3.2. MRI

MRI is superior than MDCT in the characterization of pheocromocitoma and carcinoma infiltration.

Malignant lesions show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images with strong enhancement and slow washout after contrast media administration; benign lesions usually presents isointense or low signal intensity on T1 and T2 weighted images and rapid contrast and washout after contrast media administration [40–42].

On T2-weighted images 30% of lesions presents overlapping between benign and malign tumor appearance, such as adrenal carcinoma and metastatic lesions.

The presence of calcifications, necrosis and hemorrage is suspicious but not pathognomonic for malignant lesions.

This imaging method has the same diagnostic accuracy of MDCT in the evaluation of the spread of the tumor into liver, lymph node and lung, but is better than MDCT in the evaluation of near tissue infiltration, particularly into the inferior cava vein [43,44]. The only limitation is due to the lower spatial resolution in the characterization of very small lesions.

The "*in-phase*" and "*out-of-phase*" T1 weighted GRE sequences define the Chemical Shift Phoenomenon (CSI) [25] because of the microscopic fat and water intensity signal in phase decreases in out of phase sequences. CSI could be a useful tool to differentiate benign from malignant lesions, even if some benign lesions, such as "lipid-poor adenomas" will escape this characterization. Trace of lipids could be detected also in adrenal carcinoma, but not in pheocromocitoma and these features are useful to distinguish carcinoma from pheocromocitoma [31].

4.3.3. Fine needle aspiration (FNA)

Ultrasound or, more frequently, CT-guided fine needle aspiration is a useful diagnostic tool in the evaluation of adrenal lesions [45,46]. This method is reserved in patients in whom the presence of adrenal metastases may modify therapy and/or prognosis; it is not indicated in patients with adrenal incidentaloma without risk factors for malignancy [15].

FNA may identify metastases, but it cannot differentiate adenoma from primary adrenal carcinoma [47].

If a pheocromocitoma is suspected, FNA is not indicated, because the procedure could determine hypertensive crisis or sudden death [1].

4.3.4. Management

The management of adrenal incidentaloma is still controversial because the clinician is called upon to devise a cost-effective approach taking into account the extensive endocrine work-up and radiological investigations that may be necessary [48].

A screening evaluation should be performed to exclude a functioning adrenal tumor in all patients with adrenal incidentaloma.

Although by definition an incidentaloma is a clinically silent. Mass, a careful investigation including family history and physical examination must be performed, followed by assessing the characteristics of the tumor, whether it is hormonally active or malignant [22,45]. An overnight low dose dexamethasone suppression test, the measurement of 24-h urinary catecholamines or metanephrines, serum potassium and, in hypertensive patients, upright plasma aldosterone/PRA ratio. DHEAS measurements may show evidence of adrenal androgen excess. Positive results should be followed by specific hormonal evaluations for a definitive diagnosis [15].

Laparoscopic adrenalectomy is the best choice for hormone hypersecreting type of adrenal incidentaloma with typical symptoms in patients with adrenal incidentaloma, especially if the tumor types are Conn's disease and pheochromocytoma [1,45].

Although the natural history of Subclinical Cushing's Syndrome and its morbidity are unclear, we advocate adrenalectomy for patients with this condition, especially in the presence of clinical problems (metabolic disorder such as insulin resistance, or even progressing to Cushing's syndrome) potentially aggravated by glucocorticoid excess [49].

The size of adrenal incidentaloma can be a parameter in differentiating benign and malignant tumor, although it is hormonally inactive.

The size of tumor is measured by CT or MRI. Tumor with size less than 4 cm is generally benign and adrenalectomy is not recommended; however, repeated CT scan is needed every 3–6 months on the first year and every year for 3 years period, and hormonal re-evaluation should be performed annually; then hormonal and radiological evaluation should be performed after 1 year, then every 1–2 years for a period which awaits to be defined by oncoming data from long-term follow-up of large series [50–52].

If hormonal status becomes active or the size of the tumor increases, then adrenalectomy is performed.

In patients with extra-adrenal malignancy, in particular of the lung, the AI (especially if bilateral) may be a metastasis. In this case, an FNA biopsy should be performed [15].

Features suggestive of malignancy are large size, irregular margins, non-homogeneous density and an attenuation value >20 HU on noncontrast-enhanced CT. According to our own experience a mass larger than 4 cm should be surgically removed [15].

Adrenalectomy can be performed by methods of laparatomy or laparoscopic. Tumor size and tumor malignancy status determine the surgical method, even if laparoscopic treatment has lower morbidity and mortality rate, ranges from 5 to 10% and 1–2% [53,54].

If the tumor size is less than 10 cm, laparoscopic adrenalectomy can be performed. If the tumor size is more than 10 cm, laparatomy is suggested. The surgical method-of-choice for malignancy is laparatomy [1,55].

Surgery is indicated also for lesions that grow significantly in diameter in the course of follow-up [12].

In conclusion, the prognosis of adrenal incidentaloma depends on the tumor. The majority of adrenal incidentaloma is non-hypersecreting tumor, with a good prognosis.

Approximately 20% of adrenal incidentaloma can develop into hypersecreting tumor in 3–4 years period, particularly tumor with size >3 cm [56].

The prognosis of hypersecreting tumor will get worse if no surgical measure is taken, because the possible complication due to hypersecreting hormone. Prognosis after surgical removal of

hypersecreting tumor is generally good, because the removal can decrease cardiovascular risk such as hypertension, hyperglycemia and hypercholesterolemia [56].

The prognosis of tumor metastases depends on histological profile, staging and location of the primary tumor. The worst prognosis is for adrenocortical carcinoma with >6 cm diameter.

Ethical approval

Ethical approval was requested and obtained from the "Azienda Universitaria SUN" ethical committee.

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Author contribution

Alfonso Reginelli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Graziella Di Grezia: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and co-editing of the manuscript.

Alfredo D'andrea: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Andrea Izzo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Salvatore Cappabianca: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Ettore Squillaci: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Roberto Grassi: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially editing of the manuscript.

Conflict of interest

All authors have no conflict of interests.

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